AMENDMENTS TO THE SPECIFICATION

Please insert the accompanying Sequence Listing (pages 1-109).

Please amend the paragraph at page 14, line 6 through page 15, line 4, as follows:

Figures 1A, 1B, and 1C show an HPLC analysis of the D-NorFES-A protease indicator (F^1-Asp-Ala-Ile-Pro-Nle-Ser-Ile-Pro-Cys-F^2, SEQ ID NO:1) where F^1 is a donor (D) fluorophore (5'-carboxytetramethylrhodamine (C2211) and F^2 is an acceptor (A) fluorophore (rhodamine X acetamide (R492))) before and after the addition of elastase. Fig. 1A: HPLC before the addition of elastase showing the late eluting peak representing the intact indicator molecule. Fig. 1B: HPLC after the addition of elastase with detection at 550 nm where both fluorophores absorb. Fig. 1C HPLC after the addition of elastase with detection at 580 nm where F^2 absorbs maximally.

Please amend the paragraph at page15 line 17 through page 16, line 7, as follows:

Figure 5 illustrates fluorescence of a DEVD, a DEVN, and an ICE substrate. To one hundred µl of assay buffer (50mM HEPES buffer pH 7.5, 10% (w/v) sucrose and 0.1% (w/v) CHAPS) containing 1µM of substrate DEVD (compound 2 of Example 8), DEVN (compound 3 of Example 8) and ICE (compound 5 of Example 8) 10µl of Jurkat cell lysate was added and incubated for 16 hours at 37°C. The Jurkat cells' lysate was prepared from the cells that had been stimulated by antiFas antibody at 1µg/ml concentration for 6 hours. The fluorescence intensity for the substrate solution alone is indicated in Figure 5 as a horizontal lined bar marked as t = 0 hr and the fluorescence intensity of the lysate and substrate solution mixture after 16 hr is indicated by vertical line bar and is marked as t = 16 hr digestion. 10 µl cell lysate was pre-incubated with 50 µm ZVAD-FMK (benzyoxycarbonyl valanyl alanyl aspartyl-fluoromethylketone) at 37°C for 30 min. then added to the substrate solution. The fluorescence intensity after 16 hours for this mixture is indicated by the bar marked as ZVAD-FMK (inhibitor). Lastly, pre-incubated cell lysate with iodoacetamide(alkylating agent for sulfhydryl group) and PMSF (for inhibiting serine proteases) was added to the substrate solution. The fluorescence intensity after 16 hours at 37°C is indicated by bar marked as Iodoacetamide/PMSF. The DEVN substrate is a negative control substrate where the P1, Asp, residue is replaced by Asn. The CPP32 protease requires the P1 residue to be aspartic acid residue. The four bar graphs for the DEVN substrate (Fig. 5) clearly indicate that the activated cell lysate do not contain any other protease that digest the DEVD substrate, since the intensity for 16 hour digestion is the same as the substrate alone.

The bar graphs for the DEVD substrate indicate that the activate cell lysate do contain CPP32 protease and this protease activities are inhibited by ZVAD-FMK, known CPP32 protease inhibitor. The contribution of any other proteases in digesting DEVD substrate is very small as indicated by the difference between the intensities of ZVAD-FMK bar to Iodoacetamide/PMSF bar.

Please amend the paragraph at page 21, lines 1-8, as follows:

In certain preferred embodiments, the protease binding region of the protease indicators of the present invention is selected to be symmetric about the cleavage site. Thus, for example, where a binding region is:

Ile-Pro-Met-Ser-Ile (SEQ ID NO:2)

(*e.g.* α-1 anti-trypsin) and the cleavage occurs between Met and Ser then a four amino acid residue binding region based on this sequence would be:

- P_2 -P_1 - P_1'- P_2'-
-Pro-Met-Ser-Ile- (SEQ ID NO:3)

Please amend the paragraph at page 21, lines 14-21, as follows:

Various amino acid substitutions may be made to the amino acids comprising the protease binding domain to increase binding specificity, to eliminate reactive side chains, or to reduce the conformational entropy (decrease degrees of freedom) of the molecule. Thus, for example, it is often desirable to substitute methionine (Met) residues, which bear a oxidizable sulfur, with norleucine. Thus, in the example given, a preferred protease binding region will have the sequence:

- P_2- P_1 - P_1'-P_2'-
-Pro-Nle-Ser-Ile- (Seq ID NO:4)

Please amend Table 2 at pages 23-25, as follows:

Table 2. Illustration of the design of the conformation determining regions and protease binding site based on known protease substrate and inhibitor sequences. Italics indicate residues that are added to create a bend and to increase rigidity of the conformation determining regions. Normal font indicates

residues of the substrate or inhibitor that forms the protease binding site. The thick line indicates the location at which the protease binding site is cleaved.

Substrate/Inhibitor	CDR (C^1)			Protease Binding Site (P) P_2				CDR (C^2)		SEQ ID NO
	C^1_5	C^1_4	C^1_3		P_1	P_1'	P_2'	C^2_3	C^2_4	
α-1 anti-trypsin	*Asp*	*Ala*	Ile	Pro	Met *Nle*	Ser	Ile	*Pro* *Aib*	Cys Lys	5
plasminogen activator inhibitor 2	*Asp*	Met *Aib* Pro	Thr *Aib* *Pro*	Gly	Arg	Thr	Gly	*Pro* *Aib*	Cys Lys	6
neutrophil leukocyte elastase inhibitor	*Asp*	Ala *Aib*	Thr *Aib* *Pro*	Phe	Cys	Met *Nle*	Leu	*Pro* *Aib*	Cys Lys	7
anti-plasmin inhibitor	*Asp*	*Aib*	Ser *Aib* *Pro*	Arg	Met *Nle*	Ser	Leu	*Pro* *Aib*	Cys Lys	8
anti α-1 thrombin	*Asp*	Ile *Aib*	Ala *Aib* *Pro*	Gly	Arg	Ser	Leu	*Pro* *Aib*	Cys Lys	9
α-1 antichymotrypsin	*Asp*	*Aib*	Thr *Aib* *Pro*	Leu	Leu	Ser	Leu	*Pro* *Aib*	Cys Lys	10
interstitial type III (human liver) collagen	*Asp*	Gly *Aib*	Pro *Aib*	Leu	Gly	Ile	Ala	*Pro* *Aib*	Cys Lys	11
type I collagen for collagenase Bovine α 1	Asp	Gly *Aib* *Pro*	Pro *Aib*	Gln	Gly	Ile	Leu	*Pro* *Aib*	Cys Lys	12
type I collagen chick α2	Asp	Gly *Aib* *Pro*	Pro *Aib*	Gln	Gly	Leu	Leu	*Pro* *Aib*	Cys Lys	13
human α1 type II collagen	Asp	Gly *Aib* *Pro*	Pro *Aib*	Gln	Gly	Ile	Ala	*Pro* *Aib*	Cys Lys	14
type III collagen - AIA	Asp	Gly *Aib* *Pro*	Pro *Aib*	Gln	Ala	Ile	Ala	*Pro* *Aib*	Cys Lys	15
type III collagen (human skin)	*Asp*	Gly *Aib* *Pro*	Pro *Aib*	Gln	Gly	Ile	Ala	*Pro* *Aib*	Cys Lys	16
human α 2 macroglobulin	*Asp*	Gly *Aib* *Pro*	Pro *Aib*	Glu	Gly	Leu	Arg	*Pro* *Aib*	Cys Lys	17
stromelysin cleavage sites of stromelysin-1d	*Asp*	Asp *Aib* *Pro*	Val *Aib* *Pro*	Gly	His	Phe	Arg	*Pro* *Aib*	Cys Lys	18
stromelysin cleavage sites of stromelysin-1	*Asp*	Asp *Aib* *Pro*	Thr *Aib* *Pro*	Leu	Glu	Val	Met *Nle*	*Pro* *Aib*	Cys Lys	19
stromelysin cleavage site	*Asp*	Arg	Ala	Ile	His	Ile	Gln	*Pro*	Cys	20

of proteoglycan link protein		*Aib* *Pro*	*Aib* *Pro*					*Aib*	Lys	
gelatinase type IV collagenase site of 72 K gelatinases	*Asp*	Asp *Aib* *Pro*	Val *Aib* *Pro*	Ala	Asn	Tyr	Asn	*Pro* *Aib*	Cys Lys	21
gelatinase type IV cleavage of gelatin	*Asp*	Gly *Aib* *Pro*	Pro *Aib*	Ala	Gly	Glu	Arg	*Pro* *Aib*	Cys Lys	22
gelatinase type IV cleavage of gelatin	*Asp*	Gly *Aib* *Pro*	Pro *Aib*	Ala	Gly	Phe	Ala	*Pro* *Aib*	Cys Lys	23
type III collagen (human skin)	*Asp*	Gly *Aib* *Pro*	Pro *Aib*	Gln	Gly	Leu	Ala	*Pro* *Aib*	Cys Lys	24
Human FIB-CL propeptide	*Asp*	Asp *Aib* *Pro*	Val *Aib* *Pro*	Ala	Gln	Phe	Val	*Pro* *Aib*	Cys Lys	25
Cathepsin D (Thyroglobulin Fragment Tg1)	Asp	Asp Aib Pro	Gly Pro Aib	His	Phe	Leu	Arg	*Pro* *Aib*	Cys Lys	26
Cathepsin D (Thyroglobulin Fragment Tg2)	Asp	Thr Aib Pro	Thr Pro Aib	Glu	Leu	Phe	Ser	*Pro* *Aib*	Cys Lys	27
Cathepsin D (Thyroglobulin Fragment Tg3)	Asp	Lys Aib Pro	Phe Pro Aib	leu	Ala	Phe	Leu	*Pro* *Aib*	Cys Lys	28
Cathepsin D (Thyroglobulin Fragment Tg4)	Asp	Phe Aib Pro	Ser Pro Aib	His	Phe	Val	Arg	*Pro* *Aib*	Cys Lys	29
Prostate Specific Antigen (PSA) (Seminolgelin, Sg) Sg1	Asp	Gln Aib Pro	Gln Pro Aib	Leu	Leu	His	Asn	*Pro* *Aib*	Cys Lys	30
Prostate Specific Antigen (PSA) (Seminolgelin, Sg) Sg2	Asp	Ser Aib Pro	Ile Pro Aib	Gln	Tyr	Thr	Tyr	*Pro* *Aib*	Cys Lys	31
Prostate Specific Antigen (PSA) (Seminolgelin, Sg) Sg3	Asp	Ser Aib Pro	Ser Pro Aib	Gln	Tyr	Ser	Asn	*Pro* *Aib*	Cys Lys	32
Prostate Specific Antigen (PSA) (Seminolgelin, Sg) Sg4	Asp	Ser Aib Pro	Ser Pro Aib	Ile	Tyr	Ser	Gln	*Pro* *Aib*	Cys Lys	33
Gelatin α1 (type 1)	*Asp*	Gly *Aib* *Pro*	Pro *Aib*	Ala	Gly	Val	Gln	*Pro* *Aib*	Cys Lys	34

Please amend the paragraph at page 26, lines 21-34, as follows:

In a particularly preferred embodiment, aa^1 and aa^{10} are independently selected from the group consisting of lysine, ornithine and cysteine; aa^2, aa^3, aa^8 and aa^9 are independently selected from the group consisting of an amino acid or a dipeptide consisting of Asp, Glu, Lys, Ornithine, Arg,

Citulline, homocitrulline, Ser, homoserine, Thr, and Tyr; aa^5, aa^4, aa^6, and aa^7 are independently selected from the group consisting of proline, 3,4-dehydroproline, hydroxyproline, alpha aminoisobutyric acid and N-methyl alanine; X is selected from the group consisting of Gly, βAla, γAbu ,Gly-Gly, Ahx, βAla- Gly, βAla-βAla, γAbu-Gly, βAla-γAbu, Gly-Gly-Gly, γAbu-γAbu, Ahx-Gly, βAla-Gly-Gly, Ahx-βAla, βAla-βAla-Gly, Gly-Gly-Gly-Gly (SEQ ID NO:35), Ahx-γAbu, βAla-βAla-βAla, γAbu-βAla-Gly, γAbu-γAbu-Gly, Ahx-Ahx, γAbu-γAbu-βAla, and Ahx-Ahx-Gly; Y is selected from the group consisting of Gly, βAla, γAbu, Gly-Gly, Ahx, Gly-βAla, βAla-βAla, Gly-γAbu, γAbu-βAla, Gly-Gly-Gly, γAbu-γAbu, Gly-Ahx, Gly-Gly-βAla,βAla-Ahx, Gly-βAla-βAla, Gly-Gly-Gly-Gly(SEQ ID NO:35), γAbu-Ahx, βAla-βAla-βAla, Gly-βAla-γAbu, Gly-γAbu-γAbu, Ahx-Ahx, βAla-γAbu-γAbu, and Gly-Ahx-Ahx.

Please amend Table 3 on page 28 as follows:

Table 3. Illustration of the design of the conformation determining regions and protease binding sites in molecules having P domains larger that 4 amino acids. The P1 residue is underlined. Z is benzyloxycarbonyl group, K[TFA] means Lys(N(epsilon)trifluoroacetyl), Fm is Fmoc (preferably attached to the alpha amino group of the amino terminal residue *e.,g.*, Lysine (K). O indicates tetrahydroisoquinoline-3-carboxylic acid. Aib, designated as B, can be replaced by Pro.

Name	aa^1	aa^2 - aa^3	aa^4	aa^5	X	P	Y	aa^6	aa^7	aa^8 - aa^9	aa^{10}	S^2	SEQ ID NO
PAI-2	K	D		B		TG<u>R</u>TG		P			K	GY	36
PAI-2(b)	K	D	P	P		TGRTG		P	P		K	GY	37
DEVD	K	D		B		DEV<u>D</u>GID		P			K	GY	38
DevN	K	D		B		DEV<u>N</u>GID		P			K	GY	39
PARP	K	D		B		EV<u>D</u>GID		P			K	GY	40
ICE	K	DY		B		A<u>D</u>GID		P			K	GY	41
Fm-DEVD	Fm-K	D		B		DEV<u>D</u>GID		P			K	GY	42
Fm-DEVN	Fm-K	D		B		DEV<u>N</u>GID		P			K	GY	43
Fm-PARP	Fm-K	D		B		EV<u>D</u>GID		P			K	GY	44
Fm-KNFES	Fm-K	D		-		AIP<u>M</u>SI		P			K	GY	45
	Fm-K	D				AIPNluSI		P			K	GY	46
Fm-G2D2D	Fm-K	D		B		GDEV<u>D</u>GID	G	P			K	GY	47

Fm-CGD2D	Fm-K	D		B	J	GDEVDGID	G J	P			K	GY	48
Z-CGD2D	Z-K	D		B	J	GDEVDGID	G J	P			K	GY	49
Fm-ICE	Fm-K	DY		B		ADGID		P			K	GY	50

Please amend Table 4, at pages 29-35, as fillows:

Table 4. Illustration of the design of the conformation determining regions and protease binding sites in molecules having P domains larger that 4 amino acids. The P1 residue is underlined. Z is benzyloxycarbonyl group, K[TFA] means Lys(N(epsilon)trifluoroacetyl), Fm is Fmoc (preferably attached to the alpha amino group of the amino terminal residue *e.,g.*, Lysine (K). O indicates tetrahydroisoquinoline-3-carboxylic acid. Aib, designated as B, can be replaced by Pro. J is a C

Substrate class	aa^1	aa^2-aa^3	aa^4	aa^5	X	P	Y	aa^6	aa^7	aa^8-aa^9	aa^{10}	S^2	SEQ ID NO
CPP32	Fa-K	D		P	JG	DEVDGIN	GJ	P			K	GY	51
CPP32	Fm-K	D		P	JG	DEVDGIN	GJ	P			K amide		52
CPP32	Fm-K	D		P	JG	(d-O)DEVDGIN	GJ	P			K	GY	53
CPP32	Fm-K	D		P	JG	DEVDGIN	G	P			K	GY	54
CPP32	Fm-K	D		P	G	DEVDGIN	GJ	P			K	GY	55
CPP32	Fm-K	D		P	JG	DEVDGID	GJ	P			K amide		56
CPP32	Fm-K	D		P	JG	EEVEGIN	GJ	P			K	GY	57
CPP32	Fm-K	D		P	JG	D(dF)VDGIN	GJ	P			K	GY	58
CPP32	Fm-K	D		P	JG	(d-D)EV(d-D)GIN	GJ	P			K	GY	59
CPP32	Fm-K	D		P	JG	DEVDGIN	GJ	P			K	GY	60
CPP32	Fm-K	DB			JG	DEVNGIN	GJ	P			K	GY	61
CPP32	Fm-K	DB			JG	DEVDGID	GJ	P			K	GY	62
CPP32	Fm-K	DB			JG	DEVDGIN	GJ	P			K	GY	63
CPP32	Fm-K	DB			JG	DEVNGID	GJ	P			K	GY	64

CPP32	K	D		B	JJ	GDEVDGID	JJ	P			K	GY	65
CPP32	K	D		B	J	GNEVDGID	GJ	P			K	GY	66
CPP32	K	D		B	J	GDEVDGIN	GJ	P			K	GY	67
CPP32	K	D		B	J	GNEVDGIN	GJ	P			K	GY	68
CPP32	K	D		B	J	GDEVNGIN	GJ	P			K	GY	69
CPP32	K	D		B	J	GNEVNGIN	GJ	P			K	GY	70
CPP32	K	D		B	JG	ODEVDGID	GJ	P			K	GK	71
CPP32	K	D		B	JG	dODEVDGID	GJ	P			K	GY	72
CPP32	K	D		B	JG	WDEVDGID	GJ	P			K	GY	73
CPP32	K	D		B	JG	dWDEVDGID	GJ	P			K	GY	74
CPP32	K	D		B	JG	dOdODEVDGID	GJ	P			K	GY	75
CPP32	K	D		B	JG	dWdWDEVDGID	GJ	P			K	GY	76
CPP32	K	D		B		YVADGID		P			K	GY	77
CPP32	K	D		B		YVADGIN		P			K	GY	78
CPP32	K	D		B		YVANGIN		P			K	GY	79
CPP32	K	D		B	G	YVADGID	G	P			K	GY	80
CPP32	K	D		B	G	YVADGIN	G	P			K	GY	81
CPP32	K	D		B	G	YVANGIN	G	P			K	GY	82
CPP32	K	D		B	JG	YVADGID	GJ	P			K	GY	83
CPP32	K	D		B	JG	YVANGID	GJ	P			K	GY	84
CPP32	K	D		B	JG	YVANGIN	GJ	P			K	GY	85
CPP32	K	D		B	JG	YVADGIN	GJ	P			K	GY	86
CPP32	K	D		B	JG	dYVADGIN	GJ	P			K	GY	87
CPP32	K	D		B		YVHDAPV		P			K	GY	88
CPP32	K	D		B		YVHDAPV		P			K	GY	89
CPP32	K	D		B		YVHDAPV		P			K	GY	90

CPP32	K	D		B	G	YVHDAPV	G	P			K	GY	91
CPP32	K	D		B	G	YVHDAPV	G	P			K	GY	92
CPP32	K	D		B	G	YVHDAPV	G	P			K	GY	93
CPP32	K	D		B	JG	YVHDAPV	GJ	P			K	GY	94
CPP32	K	D		B	JG	YVHDAPV	GJ	P			K	GY	95
CPP32	K	D		B	JG	YVHDAPV	GJ	P			K	GY	96
CPP32	K	D		B	JG	YVHDAPV	GJ	P			K	GY	97
CPP32	K	D		B	JG	YVHDAPV	GJ	P			K	GY	98
CPP32	K	D		B	JG	dYVHDAPV	GJ	P			K	GY	99
Lamin-A	Fm-K	D		P	JG	LVEIDNG	J	P			K	GY	100
Lamin-A	FM-K	DP			JG	LVEIENG	J	P			K	GY	101
Lamin-A	K	D		B		LVEIDNG		P			K	GY	102
Lamin-A	K	D		B	G	LVEIDNG	G	P			K	GY	103
Lamin-A	K	D		B	JG	LVEIDNG	GJ	P			K	GY	104
Lamin-A	K	D		B	JG	LVEINNG	GJ	P			K	GY	105
ProCPP32Asp175	Fm-K	D		P	J	GIETESGV	GJ	P			K	GY	106
ProCPP32Asp175	Fm-K	D		P	J	GIETDSG	J	P			K	GY	107
ProCPP32Asp175	Fm-K	D		P	J	GIETESG	J	P			K	GY	108
ProCPP32Asp175	K	D		B		GIETDSGVDD		P			K	GY	109
ProCPP32Asp175	K	D		B		GIETNSGVDD		P			K	GY	110
ProCPP32Asp175	K	D		B	G	GIETDSGVDD	G	P			K	GY	111
ProCPP32Asp175	K	D		B	G	GIETNSGV	G	P			K	GY	112
ProCPP32Asp175	K	D		B	J	GIETDSGV	J	P			K	GY	113
ProCPP32Asp175	K	D		B	J	GIETNSGV	J	P			K	GY	114
ProCPP32Asp175	K	D		B	JG	GIETDSGV	GJ	P			K	GY	115
ProCPP32Asp175	K	D		B	JG	GIETNSGV	GJ	P			K	GY	116
ProCPP32Asp28	K	D		B		GSESMDSGISLD		P			K	GY	117

ProCPP32Asp28	K	D		B	G	GSESMDSG	G	P			K	GY	118
ProCPP32Asp28	K	D		B	JG	GSESMDSG	GJ	P			K	GY	119
NS3 NS5A/5B	K	D		B	JG	DVVCCSMS	GJ	P			K	GY	120
NS3 NS5A/5B	K	D		B	JG	DVVCDSMS	GJ	P			K	GY	121
NS3 NS5A/5B	K	D		B	JG	DVVCCSdMS	GJ	P			K	GY	122
NS3 NS5A/5B	K	D		B	JG	DVVCDSdMS	GJ	P			K	GY	123
NS3 NS5A/5B	K	D		B	JG	DVVCCPdMS	GJ	P			K	GY	124
NS3 NS5A/5B	K	D		B	JG	EDVVCCS	GJ	P			K	GY	125
NS3 NS5A/5B	K	D		B	JG	EDVVCDS	GJ	P			K	GY	126
NS3 NS5A/5B	K	D		B	JG	EDdVVCCP	GJ	P			K	GY	127
NS3 NS5A/5B	K	D		B	JG	EDdVVCDP	GJ	P			K	GY	128
NS3 NS5A/5B	K	D		B	JG	DdVVCCSdMS	GJ	P			K	GY	129
NS3 NS5A/5B	K	D		B	JG	DVdVCDSdMS	GJ	P			K	GY	130
NS3 NS5A/5B	K	D		B	JG	DdVVCCPdMS	GJ	P			K	GY	131
NS3 NS5A/5B	K	D		B	JG	DVVCCSM	GJ	P			K	GY	132
NS3 NS5A/5B	K	D		B	JG	DVVCDSM	GJ	P			K	GY	133
NS3 NS5A/5B	K	D		B	JG	VCCSM	GJ	P			K	GY	134
NS3 NS5A/5B	K	D		B	JG	VCDSM	GJ	P			K	GY	135
NS3 NS4A/4B	K	D		B	JG	DEMEECSQHL		P			K	GY	136
NS3 NS4A/4B	K	D		B	JG	DEMEECPQHL		P			K	GY	137
NS3 NS4A/4B	K	D		B	JG	DEMEEDSQHL		P			K	GY	138
NS3 NS4A/4B	K	D		B	JG	EMEECSQHL		P			K	GY	139
NS3 NS4A/4B	K	D		B	JG	EMEECPQHL		P			K	GY	140
NS3 NS4A/4B	K	D		B	JG	EMEEDSQHL		P			K	GY	141
NS3 NS4A/4B	K	D		B	JG	EMEECSQHL	G	P			K	GY	142
NS3 NS4A/4B	K	D		B	JG	EMEECPQHL	G	P			K	GY	143

NS3 NS4A/4B	K	D		B	JG	EMEEDS QHL	G	P			K	GY	144
NS3 NS4A/4B	K	D		B	JG	EMEECS QHL	GJ	P			K	GY	145
NS3 NS4A/4B	K	D		B	JG	EMEECP QHL	GJ	P			K	GY	146
NS3 NS4A/4B	K	D		B	JG	EMEEDS QHL	GJ	P			K	GY	147
Ext. PAI-2	K	D		B	JG	VMTGRT G	J	P			K	GY	148
Ext. PAI-2	K	D		B	JG	VdMTGR TG	J	P			K	GY	149
Ext. PAI-2	K	D		B	JG	VMTGRT G	J	P			K	GY	150
Ext. PAI-2	K	D		B	JG	VMTGRT G	J	P			K	GY	151
Thromb	K	D		B	JG	VMTGRG	J	P			K	GY	152
Thromb	K	D		B	JG	VMTGRG	GJ	P			K	GY	153
Thromb	K	D		B	JG	VdmTGR G	GJ	P			K	GY	154
Urokinase	Fm-K	D		P	J	TGRT							155
Urokinase		Fm-D		P		TGRT	G	P			K	GY	156
Urokinase	Fm-K	D		P		VMTGRT	GJ	P			K	GY	157
Urokinase	Fm-K	D		P		TGRT	GJ	P			K	GY	158
Urokinase	Fm-K	D		P	JG	TGRT	GJ	P			K	GY	159
Urokinase	Fm-K	D		P	JG	TGRT	G	P			K	GY	160
Urokinase	Fm-K	D		P	G	TGRT	G	P			K	GY	161
Urokinase	K	D		P	J	TGRTG	J	P			K	GY	162
Urokinase	K	D		P	C3	TGRTG		P			K	GY	163
Urokinase	K	D		P	C7	TGRTG		P			K	GY	164
Urokinase	K	D		B	JG	VMTGRV G	J	P			K	GY	165
Urokinase	K	D		B	JG	VdMTGR VG	J	P			K	GY	166
F12A	K	D		B	JG	VMTGRA G	J	P			K	GY	167
F12A	K	D		B	JG	VdMTGR AG	J	P			K	GY	168
Swedish KM/NL amyloid	Fm-K	D		P	JG	SEVKLD AEF GC5 PKGY	GJ	P			K	GY	169
Swedish KM/NL	Fm-K	D		P	JG	S(d-E)VK (d-L)DA	GJ	P			K	GY	170

amyloid						E(d-F)							
Swedish KM/NL amyloid	Fm-K	D		P	JG	S(d-E)VK (d-L)DA E(d-F)	GJ	P			K	GY	171
Swedish KM/NL amyloid	K	D		B	JG	SEVNLD AEF	GJ	P			K	DD Y	172
Swedish KM/NL amyloid	Fm-K	D		B	JG	SEVNLD AEF	GJ	P			K	DD Y	173
Swedish KM/NL amyloid	K	D		B	JG	SEVKLD AEF	GJ	P			K	DD Y	174
Native Amyloid	K	D		B	JG	SEVKMD AEF	GJ	P			K	DD Y	175
Cathepsin G	K	D		B	JG	SEVKMD DEF	GJ	P			K	DD Y	176
Cathepsin G	K	D		B	JG	SEVNLD DEF	GJ	P			K	DD Y	177
APP[709-710]	K	D		B	JG	GVVIATV IVIT	GJ	P			K	DD Y	178
APP[708-719]	K	D		B	JG	YGVVIAT VIVIT	GJ	P			K	DD Y	179
APP[711-716]	K	D		B	JG	VIATVI	GJ	P			K	DD Y	180
APP[708-713]	K	D		B	JB	YGVVIA	GJ	P			K	DD Y	181
PSA Sg1	K	D		B	JJ	QQLLHN	JJ	P			K		182
PSA Sg1	K	D		B	JG	QQLLHN	GJ	P			K		183
PSA Sg1	K	D		B	G	QQLLHN	G	P			K		184
PSA Sg1	K	D		B		QQLLHN		P			K		185
PSA Sg2	K	D		B	JJ	SIQYTY	JJ	P			K		186
PSA Sg2	K	D		B	JG	SIQYTY	GJ	P			K		187
PSA Sg2	K	D		B	G	SIQYTY	G	P			K		188
PSA Sg2	K	D		B		SIQYTY		P			K		189
PSA Sg3	K	D		B	JJ	SSQYSN	JJ	P			K		190
PSA Sg3	K	D		B	JG	SSQYSN	GJ	P			K		191
PSA Sg3	K	D		B	G	SSQYSN	G	P			K		192
PSA Sg3	K	D		B		SSQYSN		P			K		193
PSA Sg4	K	D		B	JJ	SSIYSQ	JJ	P			K		194
PSA Sg4	K	D		B	JG	SSIYSQ	GJ	P			K		195
PSA Sg4	K	D		B	G	SSIYSQ	G	P			K		196
PSA Sg4	K	D		B		SSIYSQ		P			K		197
Cathepsin D	Fm-K	D		P	JG	SEVNLD AEF	GJ	P			K	GY	198
Caspase-9	Fm-K	D		P	JG	LEHDGIN	GJ	P			K	GY	199
Caspase-8	Fm-	D		P	JG	LETDGIN	GJ	P			K	GY	200

	K												
Caspase-1	Fm-K	D		P	JG	WEHDGIN	GJ	P			K	GY	201
Caspase-1	Fm-K	D		P	JG	YVHDG	J	P			K	GY	202
Caspase-1	Fm-K	D		P	JG	YVHDGIN	GJ	P			K	GY	203
Caspase-1	Fm-K	D		P	JG	YVHDAPV	GJ	P			K	GY	204
Caspase-1	Fm-K	D		P	JG	YVHDAPV		P			K	GY	205
Caspase-1	Fm-K	D		P		YVHDAPV	GJ	P			K	GY	206
Caspase-1	Fm-K	D		P	JG	YVHDA		P			K	GY	207
Granzyme B	Fm-K	DP			JG	IEPDS	GJ	P			K	GY	208
Collagenase	Fm-K	DP			JG	PLGIAGI	GJ	P			K	GY	209
HIV-1 protease	Fm-K	DP			JG	SQNYPIVQ	GJ	P			K	GY	210
Hepatitis C protease	Fa-K	DP			JG	EDVVCCS	GJ	P			K	GY	211

Please amend the paragraph at page 59, lines 24-27, as follows:

The P_1' residue can be changed to introduce either charged amino acid side chains or a structurally rigid, *e.g.*, proline, residue as illustrated in the Table 3, substrate sequences for Hepatitis C viral protease substrate NS3 NS5A/5B of DVVCCSMS (SEQ ID NO:212, normal substrate) and DVVCCPdMS (SEQ ID NO:213, inhibitor). The underlined residues are the P_1 residues.

Please amend the paragraph at page 63, lines 8-11, as follows:

Fluorophores were linked to the amino terminus via the α-amino group of Aspartic acid residue (D) and to the ε-amino group of lysine (K). Labeling was accomplished by the displacement of a succinimidyl group linked to 6-TMR or DER. The structure of the peptide, called NorFES-KGY (SEQ ID NO:214) is:

Please amend the paragraph at page 65, lines 11-20, as follows:

In addition, (homodoubly-labeled) PAI-2, CS-1 (a 31 residue long peptide) and two DEVD-like peptides were synthesized and derivatized. PAI-2 and CS-1 allowed the dye-dye dimer formation. The CS-1 peptide showed that in a significantly longer peptide the dye-dye dimer structure

can be formed. Note this peptide contained four proline residues in the amino terminal side of the putative cleavage site Ile-Leu bond. There was one proline in the carboxyl domain as well. The results from the CS-1 peptide support a potentially larger sequence between the two dyes (fluorophores). Two DEVD-like peptide's amino acid sequences that did not allow the formation of productive H-type dimers are F_1-DEVDGIDPK[F_1]GY (SEQ ID NO:~~186~~215) and F_1-PDEVDGIDPK[F_1]GY (SEQ ID NO:~~187~~216).

Please amend Table 12 at page 66, lines 1-5, as follows:

Table 12. Compounds assayed for cellular uptake. Abbreviations used in the following table are: F^1: carboxytetramethylrhodamine; Z: benzyloxycarbonyl group; Fm: Fmoc group; K[F1]: F^1 is covalently attached through the epsilon amino group of lysine (K). Single letter amino acid residues are used in the sequences except for Nlu for norleucine, B for aminoisobutyric acid and J for epsilon amino caproic acid residue. H: HPLC, FM: Fluorescence microscopy, FC: flow cytometry.

	Structure	Cellular uptake/ magnitude	Uptake checked by	SEQ ID NO
1	Fm-K[F1] DAIPNluSIPK[F1]GY	Yes/high	FM	~~188~~217
2	K[F1] DAIPNluSIPK[F1]GY	Yes/weak	FM	~~189~~218
3	Fm-DAIPNluSIPK[F1]GY	No/	FM	~~190~~219
4	Fm-K[F1]DBDEVDGIDPK[F1]GY	Yes/high	FM & FC	~~191~~220
5	K[F1]DBDEVDGIDPK[F1]GY	Yes/weak	FM	~~192~~221
6	Fm-K[F1]DBDEVNGIDPK[F1]GY	Yes/high	FM	~~193~~222
7	K[F1]DBDEVNGIDPK[F1]GY	Yes/weak	FM & H	~~194~~223
8	Fm-K[F1]DBEVDGIDPK[F1]GY	Yes/high	FM & FC	~~195~~224
9	K[F1]DYBADGIDPK[F1]GY	Yes/weak	FM	~~196~~225
10	Fm-K[F1]DBGDEVDGIDGPK[F1]GY	Yes/high	H & FC	~~197~~226
11	Fm-K[F1]DBJGDEVDGIDGJPK[F1]GY	Yes/high	FC	~~198~~227
12	Z-K[F1]DBJGDEVDGIDGJPK[F1]GY	Yes/weak	FM	~~199~~228
13	Fm-K[F1]DYBADGIDPK[F1]GY	Yes/high	FM	~~200~~229

14	K[F1]DBEVDGIDPK[F1]GY	Yes/weak	FM	~~201~~ 230

Please amend the paragraph at page 67, lines 15-26, as follows:

The elastase substrate, Fm-K[F1]DAIPNluSIPK[F1]GY (SEQ ID NO:231), (where F1 was carboxytetramethylrhodamine, Fm was Fmoc, K[F1] was F1 covalently attached through the epsilon amino group of lysine (K), and Fm-K is the Fmoc group covalently attached at the alpha amino group of the amino terminal lysine residue) was used with HL-60 cells. Cells were incubated with various concentrations of elastase substrate ranging from 10 nM to 10 μM for 5 minutes to 60 minutes. Then the cells were diluted 5-fold with RPMI 1640 medium containing 5% serum or with phosphate buffered saline. The samples were centrifuged and washed once more with 1 ml of washing solution. After centrifugation and removal of the washing solution, cell pellets were loosened with about 25 ul of medium and these cells were transferred to a glass capillary. Capillary tubes were then placed on a glass microscope slide and examined under a fluorescence microscope using standard rhodamine filters.

Please amend the paragraph at page 68, lines 12-29, as follows:

Control cells without substrate incubation and the sample with the greatest expected fluorescence signals were used to set the instrument detector parameters. For example after 15 minutes incubation of Jurkat cells with substrate compound #11 Fm-CGD2D: Fm-K[F1]DBJGDEVDGIDGJPK[F1]GY (SEQ ID NO:~~4~~232, where F1 was carboxytetramethylrhodamine; Fm was Fmoc, K[F1] was F1 covalently attached through the epsilon amino group of lysine (K), Nlu was norleucine, B was aminoisobutyric acid, and J was epsilon-aminocaproic acid) an increase of about 10 channels indicating cellular uptake of the substrates was measured. Note substrate #11 was not completely quenched. Hence, a small amount of background fluorescence would be expected from the intact substrate. Signals from the cells that had been activated with 1 μg/ml of ant-Fas antibody, CH11 clone for 1 to 6 hours indicated an increase in peak channel number. As much as a ten-fold increase in fluorescence intensity was observed. When the cells were co-incubated with the CPP32 protease inhibitor ZVAD-fluoromethylketone at 50 μM along with an apoptosis inducing agent, *e.g.*, anti-Fas antibody, this observed increase in fluorescence intensity was eliminated. This indicated that the signal from compound 11 was due to the CPP32

protease activity which was inhibitable by ZVAD-FMK. Hence, the observed fluorescence intensity in each cell as determined by flow cytometric analysis served as a direct measure of the intracellular CPP32 protease activity.

Please amend the paragraph at page 69, lines 18-27, as follows:

Jurkat cells are normally grown in 10% fetal calf serum containing RPMI 1640, at 37°C in a 5% CO_2 atmosphere. When the serum content was dropped to 4%, the Jurkat cell growth rate not only slowed down but also a significant number of cells died within 36 hours. The cell density used was about 400,000 cell per ml. After 36 hours, control wells contained about 50% dead cells (trypan blue-positive cells), whereas the wells containing 0.1 or 1.0 μM concentration of compound #11 (Table 12) "Fm-CGD2D" or Fm-K[F1]DBJGDEVDGIDGJPK[F1]GY (SEQ ID NO:~~6~~ 233) showed only 10% or 8% nonviable cells. Hence, compound #11 which exhibits efficient cellular uptake slowed down apoptosis in these Jurkat cells where it acted as a CPP32 protease inhibitor or a CPP32 activating protease inhibitor.

Please amend the paragraph at page 71, line 25 through page 72, line 19, as follows:

The parent compound Fm-DEVD has the following composition: Fmoc-K[F1]DBDEVDGIDPK[F1]GY (SEQ ID NO:~~7~~ 234). The bold face underlined letters are the protease recognition sequence consisting of 7 amino acid residues. Compound #10 contains two glycine extensions at both ends of this protease recognition sequence. The central protease recognition domain now is 8 residues long GDEVDGID (SEQ ID NO:~~8~~ 235), since the glycine residue at the amino terminus is a part of native sequence. The two glycine residues which are inherently more flexible than other amino acids, *e.g.*, alanine, provide less conformational constraint or, conversely, more flexibility than compound 4 (Table 12) and thereby permit greater flexion when combined with Aib or Pro residues. Additional insertion of amino caproic acid at both termini with five methylene groups in addition to the one present in glycine provides further relaxation of the constrained conformation and, thus, greater flexibility for the protease recognition domain, GDEVDGID (SEQ ID NO:~~9~~ 236). This progression of flexibility resulted in an increased hydrolysis rate with the CPP32 protease since CPP32 recognizes a more flexible protease recognition domain than does elastase. Support for this statement is that the CPP32 protease cleavage site in the proform of its physiological substrate, poly(ADP-ribose) polymerase, PARP, is located between two well-folded domains. . In addition, the cleavage site within

the inactive proform of CPP32 which is a member of proteases family called caspases by another caspase family member protease, caspase-8, has been shown to localized between the two folded domains of CPP32 called p17 and p12. Hence, it is expected that such a protease cleavage site would not be rigidly held or its conformation would be expected to be less defined than the remaining molecule. In order to provide these structural features to the substrate, introduction of flexible residues such as glycine, epsilon amino caproic acid, beta alanine, and amino butyric acid would be expected to play important roles in regulating the backbone flexibility of the substrate's central protease recognition domain. These additional preferred residues for the conformation determining domain are also expected to provide the needed bend-inducing influence.

Please amend the paragraph at page 72, lines 26-32, as follows:

These examples provide a tetrapeptide and a pentapeptide comprising Lys-Asp-Aib-Gly (SEQ ID NO:237) or Lys-Asp-Aib-Ahx-Gly (SEQ ID NO:238) where Ahx is episilon amino caproic acid (*i.e.* NH_2-$(CH_2)_5$-COOH). The fluorophore is attached to episilon amino group of the lysine residue. The carboxyl terminal CDR domain is defined as a tripeptide Gly-Pro-Lys and a tetrapeptide Gly-Ahx-Pro-Lys (SEQ ID NO:239). The hydrolysis rate was increased by 3-fold between compounds 4 (Fm-DEVD: Fm-K[F1]DBDEVDGIDPK[F1]GY (SEQ ID NO:~~9~~ 240)) and 10 (Fm-G2D2D: Fm-K[F1]DBGDEVDGIDGPK[F1]GY] (SEQ ID NO:~~10~~ 241))

Please amend the paragraph at page 72, line 33 through page 73, line 3, as follows:

As illustrated in Figure 5, the hydrolysis rate was further increased by *ca.* 3-fold over the above glycine residue insertion with the amino caproic amino acid (Ahx) addition, compound 11 (Fm-CGD2D: Fm-K[F1]DB Ahx GDEVDGIDG Ahx PK[F1]GY, (SEQ ID NO:~~10~~ 242). Hence, overall at least a 9-fold increase in substrate hydrolysis rate was accomplished (compounds 4 and 11, Table 12).